

Clinical Outcomes and Toxicity After Extracranial Stereotactic Body Radiotherapy for Pediatric Malignancies in a Two Center Retrospective Study

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Research Article

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Abstract

Background

Stereotactic body radiotherapy (SBRT) in pediatric malignancies offers precise, high-dose radiation delivery to tumors while minimizing exposure to surrounding healthy tissues—an important consideration in preventing adverse effects on growth and development. The use of SBRT in pediatric oncology has been increasing; however, clinical data and outcome reports remain limited. This study aimed to evaluate local control (LC), progression-free survival (PFS), overall survival (OS), and toxicity rates following SBRT in pediatric patients with extracranial metastases.

Materials/Methods

Between 2012 and 2024, 21 pediatric patients treated in our department for extracranial lesions of malignant tumors using linear accelerator–based, CT-guided SBRT were retrospectively analyzed. LC and OS were assessed using the Kaplan–Meier method.

Results

All patients received definitive SBRT for oligometastatic disease. At diagnosis, 13 patients (61.9%) presented with metastatic disease. The median follow-up time was 10 months (range, 4–157), and the median age was 13 years (range, 4–17). Ewing sarcoma was the most common histologic subtype (52.4%).

A total of 37 extracranial lesions were irradiated; 21 (56.7%) were bone metastases. SBRT was delivered to four sites in one patient and to three simultaneous sites in five patients. The median number of fractions was 5 (range, 3–5), with a median dose per fraction of 5 Gy (range, 5–9 Gy). Median BED₁₀ and EQD₂ were 37.5 Gy (31.25–72) and 31.2 Gy (31.2–60), respectively. The median PTV volume was 68 cm³ (range, 2.1–541 cm³). Median PFS was 8 ± 1.29 months (95% CI: 5.4–10.5), and median OS was 12 ± 3.07 months (95% CI: 5.98–18). Local recurrence occurred in 10 patients (47.6%), of whom 6 (60%) had in-field recurrences. Among these, 3 of 6 patients had osteosarcoma histology. One- and two-year LC rates were 25% and 18%, respectively, while OS rates were 49% and 30%. There was a statistically significant difference in both PFS and OS among histologic subtypes ($p = 0.03$ and $p = 0.004$, respectively). No ≥Grade 3 acute or late toxicity was observed.

Conclusion

SBRT was well tolerated in pediatric patients, with minimal toxicity. However, longer follow-up is required to assess late effects. The preference for more moderate fractionation schemes due to large tumor volumes and younger age groups may also be related to higher rates of in-field recurrence in histologies that are more resistant to radiotherapy. Further studies are warranted to establish the optimal SBRT dose and fractionation parameters for pediatric malignancies.

INTRODUCTION

Radiotherapy is an indispensable component of both curative and palliative treatment approaches in childhood malignancies. However, to minimize the potential adverse effects of radiotherapy on growth and development in pediatric patients, modern high-precision radiotherapy techniques have gained increasing importance.

One such technique is stereotactic body radiotherapy (SBRT), a noninvasive treatment modality that allows the delivery of high doses of radiation to the targeted tumor volume with millimetric accuracy, typically in 1–5 fractions. With the use of advanced imaging technologies and modern radiotherapy planning systems, SBRT enables the administration of highly conformal and ablative radiation doses to the tumor while minimizing exposure of surrounding healthy tissues.

The ablation-like effect of SBRT as an alternative to surgery, together with its potential immunological mechanisms and noninvasive nature, represents major advantages of this technique. High local control rates observed in adult patients, survival benefits in oligometastatic disease, and effective symptom palliation have led to the widespread clinical application of SBRT.

In contrast, SBRT is not routinely incorporated into treatment protocols for pediatric malignancies, and the available evidence is largely limited to case series and retrospective studies. In childhood cancers, SBRT is primarily used for extracranial metastases—particularly bone metastases—for palliative purposes and to achieve long-term disease control in oligometastatic settings. Additionally, SBRT is employed for re-irradiation of residual or recurrent lesions, extracranial soft tissue tumors, and spinal or paraspinal lesions to provide palliation and local disease control.

In this study, we evaluated local control (LC), progression-free survival (PFS), overall survival (OS), and toxicity outcomes in pediatric patients who received SBRT for extracranial lesions at two institutions.

MATERIALS AND METHODS

Between 2012 and 2024, the databases of MAA Acibadem University Atakent Hospital and Istanbul University Faculty of Medicine, Çapa Hospital were retrospectively reviewed to identify pediatric patients who received SBRT for metastatic disease.

Inclusion Criteria

1. Age < 18 years and treatment delivered to an extracranial site
2. SBRT delivered in a maximum of five fractions using linear accelerator–based systems
3. A minimum follow-up duration of three months

During follow-up, progression sites were evaluated using CT, PET-CT, or MRI in cases of symptom development or suspected disease progression. Medical records were reviewed to collect data on

treatment response, acute and late toxicities, last follow-up date, and current disease status. Tumor response was assessed based on follow-up imaging studies.

Collected patient data included age, sex, ECOG performance status, primary tumor histology, date of diagnosis, presence of multiple metastases, metastasis-directed surgery, local or distant progression after SBRT, last follow-up date, and current survival status.

All patients were treated with SBRT using CT-based linear accelerator systems with daily cone-beam CT-guided image-guided radiotherapy (IGRT). Treatment-related data, including number of fractions, dose per fraction, and total prescribed dose, were recorded.

Statistical Analysis

PFS and OS were calculated using the Kaplan–Meier method. OS was defined as the interval from the first SBRT session to death from any cause or to the last follow-up date for surviving patients. LC was characterized by the absence of lesion size progression, no significant increase in contrast enhancement, and no notable increase in surrounding edema on follow-up imaging of the area treated with SBRT. Prognostic analyses according to tumor type and dosimetric factors were performed using the log-rank test. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS v23 (IBM, Armonk, NY, USA).

RESULTS

Patient Demographics and Treatment Characteristics

A total of 21 pediatric patients treated with definitive SBRT for oligometastatic or oligoprogressive disease at two centers were included. Of these patients, 23.8% (n = 5) were female and 76.2% (n = 16) were male. The median age was 13 years (range: 4–17 years).

Histopathological evaluation revealed Ewing sarcoma as the most common subtype, accounting for 52.4% (n = 11) of cases. Other histologies included osteosarcoma (28.6%, n = 6), rhabdomyosarcoma (RMS) (14.3%, n = 3), and paraganglioma (4.7%, n = 1). At diagnosis, 13 patients (61.9%) presented with metastatic disease.

A total of 37 extracranial lesions were treated with SBRT. One patient received SBRT to four distinct sites, while five patients received SBRT simultaneously to three different sites. The most frequently irradiated sites were bone metastases (59.3%), followed by organ/soft tissue and lymph node metastases.

The median planning target volume (PTV) was 68 cm³ (range: 2.1–541 cm³). The median follow-up duration from the first SBRT session was 10 months (range: 4–157 months). Patient demographics and treatment characteristics details are summarized in Table 1.

Table 1
Patient Demographics and Treatment Characteristics (n = 21)

Characteristic	Value
Number of patients	21
Age, median (range), years	13 (4–17)
Sex	
Male, n (%)	16 (76.2%)
Female, n (%)	5 (23.8%)
Histopathology	
• Ewing sarcoma, n (%)	11 (52.4%)
• Osteosarcoma, n (%)	6 (28.6%)
• Rhabdomyosarcoma, n (%)	3 (14.3%)
• Paraganglioma, n (%)	1 (4.7%)
Metastatic disease at diagnosis, n (%)	13 (61.9%)
Total extracranial lesions treated with SBRT, n	37
Distribution of irradiated lesions:	
• Bone metastases, n (%)	22 (59.3%)
• Organ / soft tissue metastases, n (%)	12 (32.4%)
• Lymph node metastases, n (%)	3 (8.1%)
PTV volume, median (range), cm ³	68 (2.1–541)
Follow-up duration, median (range), months	10 (4–157)

Local Control and Survival Outcomes

Tumor response was primarily assessed using post-SBRT PET-CT or CT imaging. During follow-up, local recurrence occurred in 10 patients (47.6%), of whom 6 (60%) experienced in-field recurrence. Among patients with in-field recurrence, histologies included osteosarcoma (n = 3), rhabdomyosarcoma (n = 1), Ewing sarcoma (n = 1), and paraganglioma (n = 1).

One- and two-year LC rates were 25% and 18%, respectively. Median PFS was 8 ± 1.29 months (95% confidence interval [CI]: 5.4–10.5), while median OS was 12 ± 3.07 months (95% CI: 5.98–18). One- and two-year OS rates were 49% and 30%, respectively.

According to histological subgroup analysis, median OS was 62 months for patients with Ewing sarcoma, 9 months for those with rhabdomyosarcoma, and 6 months for those with osteosarcoma. A statistically significant difference in OS was observed among histological subtypes, primarily driven by patients with osteosarcoma ($p = 0.004$).

A statistically significant difference in PFS was also observed among histological subtypes ($p = 0.03$). Median PFS was 19 months in patients with Ewing sarcoma, 4 months in those with rhabdomyosarcoma, and 2 months in patients with osteosarcoma and paraganglioma.

Dosimetric Outcomes

The median total prescribed dose was 25 Gy (range: 25–40 Gy). The median biologically effective dose (BED_{10}) was 37.5 Gy (range: 31.25–72 Gy), and the median equivalent dose in 2-Gy fractions (EQD2) was 31.2 Gy (r

Table 2
Dose and Fractionation Characteristics

Parameter	Value
Prescribed total dose, median (range), Gy	25 (25–40)
BED_{10} , median (range), Gy	37.5 (31.25–72)
EQD2, median (range), Gy	31.2 (31.2–60)

Ten patients received $BED \geq 40$ Gy, while eleven received $BED < 40$ Gy. Median LC duration was 8 months in the $BED \geq 40$ Gy group and 6 months in the $BED < 40$ Gy group, with no statistically significant difference between the groups ($p = 0.18$).

When analyzed according to PTV volume, 9 patients had $PTV \geq 100 \text{ cm}^3$ and 12 had $PTV < 100 \text{ cm}^3$. Median PFS was 4 months in patients with $PTV < 100 \text{ cm}^3$ and 9 months in those with $PTV \geq 100 \text{ cm}^3$; however, this difference did not reach statistical significance ($p = 0.07$). In contrast, median OS was significantly longer in patients with $PTV < 100 \text{ cm}^3$ (26 months) compared to those with $PTV \geq 100 \text{ cm}^3$ (9 months) ($p = 0.017$).

Toxicity

No grade ≥ 3 acute or late toxicities were observed. No acute toxicity greater than grade 2 was recorded. One patient developed late-onset lymphedema.

DISCUSSION

This two-center retrospective study is among the limited number of investigations evaluating the efficacy and safety of SBRT in pediatric patients. The primary finding of our study is that SBRT can be safely administered in appropriately selected pediatric patients without increasing acute toxicity, while achieving acceptable local control rates.

SBRT has become a widely used treatment modality in adult oncology, particularly for early-stage non-small cell lung cancer, prostate cancer, and limited metastatic disease [1, 2]. Numerous retrospective and prospective studies have demonstrated high local control rates and low acute and late toxicity in adult populations [3]. In contrast, the literature on pediatric SBRT remains limited [4], primarily due to the rarity of pediatric cancers, small patient numbers, long life expectancy, and concerns regarding late toxicity and adverse effects on growth and development [5]. In this context, our real-world data from two centers represent a meaningful contribution to the pediatric SBRT literature.

One of the most robust studies in pediatric SBRT is a systematic review comprising nine studies and a total of 42 pediatric/adolescent and young adult patients, which reported one- and two-year local control rates of 83.5% and 74.0%, respectively. In the same review, higher BED₁₀ values were associated with significantly improved two-year local control rates, particularly in sarcoma-dominant cohorts [6]. In our study, no correlation was identified between BED value and LC. In a multicenter SBRT cohort conducted by Tinkle et al., including 55 patients and 107 extracranial lesions, the one-year cumulative local failure rate was 25.2% (95% CI: 17.2–36.1), corresponding to an approximate one-year local control rate of 75% [7]. The local control rates observed in our study were lower than those reported in some series, which may be attributed to differences in patient populations and prescribed radiation doses.

Regarding OS outcomes, a two-center study published in 2024 including 48 patients under 30 years of age reported one-year OS rates of 70–85% and two-year OS rates of 40–60% [8]. In a multicenter prospective phase II study by Elledge et al. involving 14 patients, the one-year OS rate was 84% (95% CI: 49–96) [9]. In a major review of pediatric SBRT, the OS rate was reported as 75.4% (95% CI: 54.5–96.3) [6]. In contrast, our one- and two-year OS rates were 49% and 30%, respectively.

One of the main reasons for the relatively lower local control and OS rates observed in our cohort is the radiation dose delivered. Brown et al. reported a median prescribed dose of 40 Gy in five fractions in patients with metastatic and recurrent Ewing sarcoma and osteosarcoma [10]. Parsai et al. reported a median dose of 30 Gy in five fractions in patients with recurrent and/or metastatic sarcomas [11]. In the study by Tinkle et al., doses ranged from 12 to 45 Gy, with a median of 35 Gy in five fractions [7]. In our cohort, the median total dose was 25 Gy in five fractions. This conservative dose approach was driven by the high proportion of patients under 10 years of age, large PTV volumes treated with SBRT, and concerns regarding late toxicities associated with higher doses, including growth and developmental abnormalities, organ dysfunction, and secondary malignancy risk. Additionally, proximity to critical organs and cumulative dose constraints from prior treatments limited dose escalation in some cases. This conservative approach may have contributed to lower local control and survival outcomes.

Analysis of PFS data demonstrated that although SBRT improves local control, it has limited impact on systemic disease progression. In a broader cohort of patients under 30 years of age, the one-year PFS rate was reported as 22%, while high local control rates suggested that progression was largely driven by out-of-field disease [7]. Similarly, the low PFS rates observed in our study support the notion that PFS is primarily constrained by tumor biology and systemic dissemination.

The identification of histological subtype as a significant prognostic factor for both PFS and OS highlights the critical role of tumor biology in determining SBRT outcomes. Although osteosarcoma accounted for 28.6% of our patient population, it represented 50% of in-field recurrences, suggesting a higher risk of local failure in this subgroup. The in-field local recurrence rate was 50% (3/6) in osteosarcoma patients compared to 20% (3/15) in non-osteosarcoma histologies. Although statistical significance was not reached due to the limited sample size, this finding is clinically meaningful. The radioresistant nature of osteosarcoma has been well characterized [12], with contributing radiobiological factors including a low α/β ratio, pronounced tumor hypoxia, a heterogeneous microenvironment, and enhanced DNA repair capacity [13, 14]. These features may limit local control even with high-dose-per-fraction approaches such as SBRT.

Based on these findings, SBRT in pediatric patients should be regarded primarily as a modality for achieving local disease control, symptom palliation, and integration with systemic therapies rather than a curative approach. Appropriate patient selection, particularly in oligometastatic or oligoprogressive disease, may enhance the clinical benefit of SBRT.

The main limitations of this study include its retrospective design, limited sample size, and histological heterogeneity. In addition, the relatively short follow-up duration limits the assessment of long-term local control and late toxicity outcomes. Nevertheless, the real-world data obtained from two centers represent a major strength of our study, demonstrating the feasibility of SBRT in routine pediatric oncology practice. Particularly in carefully selected patients with oligometastatic or oligoprogressive disease, SBRT has reflected the potential to achieve meaningful local disease control with minimal toxicity. The observed survival outcomes appear to be largely influenced by tumor biology and conservative dose selection driven by concerns regarding late toxicity. All these findings emphasize the importance of individualized treatment schemes and multidisciplinary treatment decision-making in pediatric SBRT practice. Larger-scale, prospective, and histology-specific studies are needed to determine optimal patient selection and dose–fractionation strategies for pediatric SBRT.

Declarations

ETHICS STATEMENT

This study was approved by the local institutional ethics committees. Due to the retrospective nature of the study, informed consent was waived.

All procedures performed in this study involving human participants were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Clinical trial number: Not applicable.

Competing Interests

The authors declare no competing interests.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

All figures include descriptive captions to ensure accessibility.

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